Interview with Dr. Young-Ki Paik, President of the Human Proteome Organization (HUPO): Pharmacoproteomics and the Approaching Wave of "Proteomics Diagnostics"

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Abstract: Dr. Young-Ki Paik directs the Yonsei Proteome Research Center in Seoul, Korea and was elected as the President of the Human Proteome Organization (HUPO) in 2009. In the December 2009 issue of the Current Pharmacogenomics and Personalized Medicine (*CPPM*), Dr. Paik explains the new field of pharmacoproteomics and the approaching wave of "proteomics diagnostics" in relation to personalized medicine, HUPO's role in advancing proteomics technology applications, the HUPO Proteomics Standards Initiative, and the future impact of proteomics on medicine, science, and society. Additionally, he comments that (1) there is a need for launching a Gene-Centric Human Proteome Project (GCHPP) through which all representative proteins encoded by the genes can be identified and quantified in a specific cell and tissue and, (2) that the innovation frameworks within the diagnostics industry hitherto borrowed from the genetics age may require reevaluation in the case of proteomics, in order to facilitate the uptake of pharmacoproteomics innovations. He stresses the importance of biological/clinical plausibility driving the evolution of biotechnologies such as proteomics, instead of an isolated singular focus on the technology *per se*. Dr. Paik earned his Ph.D. in biochemistry from the University of Missouri-Columbia and carried out postdoctoral work at the Gladstone Foundation Laboratories of Cardiovascular Disease, University of California at San Francisco. In 2005, his research team at Yonsei University first identified and characterized the chemical structure of *C. elegans* dauer pheromone (daumone) which controls the aging process of this nematode. He is interviewed by a multidisciplinary team specializing in knowledge translation, technology regulation, health systems governance, and innovation analysis.

Keywords: Anticipatory governance, HUPO Proteomics Standards Initiative, innovation analysis, personalized medicine, pharmacoproteomics.

INTERVIEW

1. The Science of Proteomics

CPPM: Thank you for agreeing to this interview, Dr. Paik. Our readership and certainly the general public are probably far more familiar with the language and science of genomics. We're wondering if you can give us a working definition of "proteomics" and "pharmacoproteomics" and perhaps provide some examples?

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Paik: A broad working definition of proteomics may be that proteomics is a high-throughput, data-rich, comprehensive, systematic, large-scale, and quantitative analysis of the expression of proteins and their associated peptides in biological/clinical samples obtained under specific (patho) physiological settings. Thus, proteomics provides a unique means to gain insights into the relative abundance of protein components present in complex biological samples, a capability that is important for the discovery of biomarkers and novel drug targets. Pharmacoproteomics, a term that is a synthesis of "pharmacology" and "proteomics", refers to the comprehensive proteomics analysis that is relevant to novel drug target discovery, drug metabolism, as well as drug efficacy and toxicity. A systematic qualitative and quantitative monitoring of proteomics changes before and after drug treatment can be seen in many recently published papers. For example, Singh *et al*. [1] examined the protein expression using two-dimensional electrophoresis (2DE) in IB3-1 cystic fibrosis bronchial epithelial cells and identified proteins that were differentially expressed in response to treatment of these cells with 4-phenylbutyrate, a drug used to treat the urea cycle disorders. The pharmacoproteomics profiling of drug treatment provides a deeper understanding of potential side effects [2, 3], mechanism of action [4], and proteindrug/protein-protein interactions [5] by measuring the dynamic and *functional* changes in genes or proteins involved in drug metabolism and molecular drug targets.

CPPM: With the approaching wave of pharmacoproteomics, systems biology and other more "dynamic" measures of cellular physiology in health and disease, complexities and opportunities in postgenomics medicine are rapidly growing. Looking through and beyond the context of personalized drug therapy, what are the unique advantages and limitations of proteomics technology in comparison to genomics? Is pharmacoproteomics fundamentally similar or different than pharmacogenomics? It is often stated that genomics technologies offer a higher throughput at the cost of a functional read out of cellular (patho)physiology at the proteome level, whereas proteomics offers a more integrated impact of genomic variation on protein function, but at a relatively slower throughput than genomics technology platforms. How can a better understanding of genomics and proteomics approaches in tandem help overcome the artificial compartmentalization of omics technologies on the critical path to personalized medicine?

Paik: Proteomics deals with protein expression in complex clinical specimens, yielding quantitative, functional and structural profiling, e.g., of post-translational modifications (PTM), of specific proteins of interest for a diverse array of phenotypes concerning disease susceptibility, normal physiology and health intervention outcomes. In contrast, pharmacogenomics primarily deals with variability in further *upstream* elements in the biological cascade, e.g., genetic sequence and transcriptome diversity as opposed to *integrated downstream* variations in the proteome. Both pharmacogenomics and pharmacoproteomics have nonetheless been very useful for predicting the efficacy and toxicity of drug therapy and when applicable, tailoring drug therapy, with the goal of reducing side effects and enhancing efficacy. Given the close relationship between personalized medicine and biomarker development, genome-wide profiling may complement pharmacoproteomics studies. Thus, these two fields are more complementary than they are competitive or mutually exclusive. Indeed, without genomic sequence information, proteomics would face a tremendous barrier in the identification of proteins and their variants involved in disease. Thus, based on this consensus, when we say "unique advantage" of proteomics in regard to diagnosis or treatment, perhaps the proteomics approach allows us to analyse alterations in posttranslational modification of a specific biomarker that reflects the *functional signature* of human diseases at different stages before and after their clinical manifestations are apparent and measurable. Genomics, in particular sequencebased

genomics technologies, do not have this capability and cannot be used to design such dynamic disease biomarkers (e.g., the fucosylated fraction of alpha-fetoprotein, L3, is used as a useful *prognostic* marker in patients with hepatocellular carcinoma). The application of clinical proteomics through the use of, for example, a panel of blood biomarkers for diagnostic or prognostic tests will contribute towards a rational basis for future personalized medicine. Of course, like other 'omics' disciplines, proteomics has some limitations. It is noteworthy that no technical tool exists to observe protein expression in real time, in contrast to what is now routinely practiced for the analysis of gene expression through real time qRT-PCR. In addition, proteomics heavily depends on very expensive equipment (e.g., high-resolution mass spectrometer) and associated bioinformatics tools (e.g., search engines) to identify the correct proteins of interest. It is to be noted, however, that the throughput of proteomics technologies have increased appreciably with the recent introduction of protein arrays. A number of nuanced distinctions between pharmacoproteomics and its counterpart, pharmacogenomics deserve further emphasis. These include differences with respect to target molecules (protein or peptides vs. gene or mRNA), assay profile (protein modification/quantification vs. gene polymorphism/expression), and interaction pattern (direct protein-drug/protein-protein vs. predicted gene interaction/expression network/epistasis). Hancock's group [6] recently used "shot-gun proteomics" to analyse changes in protein expression in a non-small cell lung cancer cell line (EKVX cell lines) during the course of drug treatment. Their results indicate that the synergistic cytotoxicity of drugs used for cancer cell suppression can be further used for evaluation of drug therapy in cancer. In addition, multiple reaction monitoring (MRM) techniques employed in proteomics may eventually allow us to move from discovery to routine assay in clinical proteomics of cancer research. Finally, with MRM and other associated techniques, one can directly identify disease-causing protein alterations, such as protein truncation, structural modification, and changes in protein expression. Importantly, coordinated use of genomics and proteomics in tandem can offer *mechanistic triangulation* of biomarker data, and discovery and validation of diagnostic tests on the critical path to personalized health interventions, whether they concern drug treatment, nutrition or vaccines.

CPPM: Historically, proteomics technology dates back to the late 1970s, so it's actually older than genomics or high-throughput genome sequencing which developed much later as part of the Human Genome Project in 1990s [7-9]. What do you think are the reasons for the apparent delay in introduction of proteomics diagnostics compared to genomics tests in personalized medicine? Are there certain medical specialties and therapeutic areas where pharmacoproteomics offers substantial promise?

Paik: You are correct that proteomics technology is much older than many people are presently aware. However, 2DE and LC-based separation have been the most common tools used in proteomics, and the absence of mass spectrometry (MS) for high throughput identification of proteins/peptides has delayed the development of the field into its current state. In other words, the overall speed of proteomics utilization has been dependent on the development of MS. Therefore, the delay in application of proteomics to the diagnostics field can be mostly attributed to the pace of development and application of MS to the analysis of proteins and peptides. For example, methods for detection of proteins (*not* small molecules) by MS were only introduced between the late 80s and early 90s. Furthermore, the application of proteomics to the diagnostics field with regard to personalized medicine was conceptualized early this (21st) century under the theme of biomarker discovery and validation. As mentioned earlier, proteomics heavily relies on the genomics information (e.g., the human genome sequence). This information became publicly available only in 2003. In the meantime, genomics tools and molecular biology techniques have progressed without

much restriction. This has allowed scientists to mobilize all these techniques (e.g., RFLP, DNA microarrays, and SNP detection) to identify mutations and polymorphisms in samples obtained from disease tissue. One restriction that proteomics has faced is clinical specimen complexity, which may have contributed to the delay in the direct application of proteomics to clinical diagnosis such as biomarker discovery and predictive testing [10, 11]. For example, the strategy of depletion of high-abundance proteins from blood specimens became available only 5 to 6 years ago [12]. There are many factors to consider with regard to the potential promise of pharmacoproteomics in the clinical sector. For example, as opposed to genomics techniques, pharmacoproteomics shall shed light on the drug action mechanism, the elucidation of which requires detailed information on the structure and function of drug-metabolizing proteins as well as molecular drug targets. With pharmacoproteomics tools, one can view every single reaction elicited by a drug inside a cell and identify the major protein players during drug action. For example, Butler and colleagues [13] used pharmacoproteomics techniques to track down dynamic patterns in cell membrane changes, and gained other molecular insights following metalloproteinase inhibitor treatment. Because the feasibility of proteomics analyses ultimately depends on tissue access, medical specialties where this is readily feasible might conceivably be the "lowest hanging fruits" during the implementation phase of clinical pharmacoproteomics (e.g., oncology, infectious diseases, haematological disorders and possibly, dermatology).

2. The Role of the Human Proteome Organization

CPPM: You started a two-year term as the Human Proteome Organization (HUPO) President in January 2009. What role does HUPO play in advancing proteomics science? Do pharmacoproteomics and personalized medicine already represent some of the key focus areas for HUPO?

Paik: This is a quite interesting question for everyone involved in HUPO. First of all, I must give full credit to my predecessors, Drs. Sam Hanash, John Bergeron, and Rolf Apweiler. All did pioneering work in organizing the HUPO initiatives, which have been a driving force in advancing many aspects of proteomics science. For example, in 2001, HUPO started several proteomics initiatives including the Plasma Proteome Project (chaired by Gil Omenn), Proteomics Standards Initiative (PSI, chaired by Rolf Apweiler), Brain Proteome Project (chaired by Helmut Meyer), Liver Proteome Project (HLPP, chaired by Fuchu He), Antibody Initiative (chaired by Mathias Uhlen), and Glycoproteomics (chaired by Naoyuki Taniguchi). These pivotal HUPO initiatives are designed to stimulate the foundation and development of various protein standards and techniques that are commonly used for proteomics studies. Collectively, HUPO provides international and transdisciplinary leadership and a standard for dataset generation as well as tools for sharing, depositing, and retrieving proteomics data [14]. In the years following the term of John Bergeron (2nd President) and Rolf Apweiler (3rd President), identification of disease biomarkers relevant to each HUPO initiative, e.g., the liver cancer biomarkers for the Human Proteome Project (HPP) and the Human Liver Proteome Project (HLPP) have continued to grow and presently emerged as some of the key themes of the HUPO projects. Needless to say, biomarkers have become one of the most important parts of personalized medicine as well as pharmacoproteomics. Biomarkers are increasingly becoming one of the major focuses of HUPO initiatives. In terms of the technology, HUPO offers stewardship and facilitates scientific exchange and dissemination of the cutting edge techniques to improve the limits of detection, resolution, and identification of proteins present in the biological samples and mixtures. These techniques are wide ranging and include MS, chromatography, fractionation, sample preparation, and proteome informatics. The annual HUPO congress usually provides a common meeting place for all stakeholders involved in proteomics and illustrates the advancements in analytical

tools and technologies and their applications in postgenomics biology and medicine. Although pharmacoproteomics and personalized medicine are directly represented at the HUPO, these important themes have been, and will continue to be addressed within the context of clinical proteomics at the annual congresses.

CPPM: Could you tell us about the HUPO Proteomics Standards Initiative (PSI)? What are its key objectives, who is involved, and how is it structured?
Paik: The PSI defines the community standards for data representation in proteomics to facilitate data comparison, exchange, and verification [15, 16]. PSI is organized in several working groups such as Protein Separation, Mass Spectrometry, Molecular Interactions, Protein Modifications, and Proteomics Informatics. All working groups address issues of data transport (through the collaborative development of XML schemata), description by controlled vocabularies to agreed levels of detail, and deposition in databases. PSI strongly supports and encourages data sharing between such repositories. Henning Hermjakob (UK), Randall Julian (USA) and Eric Deutsch (USA) serve as the current chairpersons of the PSI. They would be an excellent resource for various stakeholders and the CPPM readership with an interest in the HUPO PSI. More details on current activities and accomplishments of HUPO PSI are available on the web as well [16]. Needless to say, such efforts to develop proteomics standards are an essential prerequisite before proteomics diagnostics can come to fruition in personalized medicine as well as for future discovery and translational research in postgenomics medicine.

3. Proteomics, Medicine, and Society
CPPM: In the *specific* context of personalized medicine and therapeutics, what are some realistic schemas under which human proteome variation and the emerging technologies might be effectively integrated with social determinants of health and clinical practice, and further reconciled with environmental and ethical issues? In a *broader* context, what are your thoughts on the emerging practice of 21st century diagnostic medicine?
Paik: First of all, in my personal opinion, human proteome variation [17], which is caused by modification of mature proteins at the cellular level and is not coded in detail by genomic information, must be distinguished from human genome variation, which causes alterations in the primary sequence of yet to be processed immature proteins. Of course, variation in both the genome and proteome is directly or indirectly involved in disease. Genome variation can easily be detected by PCR or routine molecular biological techniques, but proteome variation can only be detected by MS or other chemical methods following exhaustive separation. Thus, a more realistic schema under which human proteome variation relevant to disease could become a part of routine clinical practice would be a so-called **i**ntegrated **a**nalytical **s**ystem for **p**roteome variation (IASP), which is based on the MS-based proteomics tool. The IASP may include MRM or SRM (single reaction monitoring) for identification and quantification of post-translationally modified peptides that are directly related to certain diseases. The IASP will be very compatible with social consensus and ethical issues because it is similar to existing diagnostic procedures in medicine. However, for IASP to be integrated into routine clinical practice, we need to carry out additional work on advanced MS detection, quantification standards, and general standardization of clinical sample collection and ways in which such procedures will be acceptable to different stakeholders such as physicians, scientists, diagnostic industry, regulators and policy-makers. It is also essential to consider population health in different countries and how best to utilize proteomics in the latter context, so that the existing gaps in biotechnology between developed and developing countries are remedied or at the very least, not widened further. From a comprehensive and long-term perspective, there is a strong need for launching a Gene-Centric Human Proteome

Project (GC-HPP) through which all representative proteins (ORF) encoded by genes can be identified and quantified in a specific cell and tissue. This GC-HPP shall provide a *basic parts list* [18] of the human proteome that can serve as a "textbook" of the protein variants present in a given cell under given disease conditions. To this end, it can be noted that the study of biological variations can be further contextualized by ever present interactions with the environment in which a host (e.g., a patient) resides. In this sense, then, proteomics can also be seen as an attempt to identify environmental (including social) factors that impact human proteome variation in concert.

CPPM: Some communities are critical that personalized medicine applications will, in fact, not be a part of routine clinical medicine. They are concerned that inequities will occur with regards to access to such diagnostics, which can be expected to be expensive at first. Can you give us your thoughts?
Paik: If I understand this question correctly, with regard to routine clinical medicine where proteomics techniques are being applied to (e.g., standard MRM for disease biomarker quantification in normal and disease samples), we can consider establishing local proteomics analysis service providers through which any local clinic can request a simple proteomic analysis of patients' sample. For some analyses such as specific disease biomarker panels, each clinic can analyse a patient's sample on a disease-specific protein chip and compare the resulting pattern of readings to patterns present in a standardized database. A so-called online service might conceivably be established through the network of personalized medicine. Proteomics analytical equipment such as highresolution mass spectrometers and related software are generally very expensive, but the consumables are *not*. Perhaps the clinical proteomics society can organize some type of consortium and share those facilities and databases for routine analyses. Still, regulation of proteomics diagnostics, their equitable development and availability in the clinic from various channels (e.g., direct to consumer versus at physician's office) are areas for further social and policy reflection.

CPPM: Past experience with genetically modified organisms (GMOs), stem cell research, and other health technologies have taught us some lessons – that it is not just scientific concerns that are important to the uptake of innovative technologies. The public's perceptions of scientific, regulatory, legal, marketing, and health insurance frameworks are also important. Is HUPO prepared to address these sorts of issues, and if so, how?
Paik: Although some of my colleagues in the clinical sectors might have already addressed these issues, it is my opinion that, at the organizational level, HUPO has not yet fully prepared for this issue. Maybe this could be the starting point for considering this issue seriously.

4. Future Outlook
CPPM: Could you briefly tell us your vision of the anticipated trajectory of proteomics, personalized medicine, and the attendant role of HUPO for the next ten years? For one thing, protein expression varies over time and context and hence, will likely shift the risk assessment models in personalized medicine from a static "one-time" evaluation of risks (e.g., genotype-dependent drug toxicity, lack of efficacy) to a more dynamic, ongoing and "repeated measures approach" to risk assessment. Business models, too, may likely change in the diagnostic industry to accommodate such technical nuances that can in turn have hard impacts on the development and uptake of proteomics innovations in personalized medicine. Any thoughts in these aspects of pharmacoproteomics and proteomics diagnostics more generally?

Paik: In my view, it is very clear that proteomics and pharmacoproteomics, along with genomics/pharmacogenomics, will be integral components of personalized medicine in the continuum from discovery, translation and clinical implementation. In the context of HUPO's role in personalized medicine, HUPO may provide the community with standard samples for protein identification and quantification, Standard Operating Procedures (SOPs), education, training, and other related public services that can be effectively applied to personalized medicine. HUPO has a long standing and credible track record filling such a role, as already seen in the case of our major initiatives (e.g., HPPP, PSI, and others). A good partnership must exist between all interested groups (e.g., clinicians, proteomics scientists, and bioinformaticians) to boost the realization of proteomics as one of the engines running personalized medicine. This partnership can be promoted by HUPO, which can create a transdisciplinary forum to facilitate the confluence of personalized medicine, pharmacoproteomics and pharmacogenomics. Business and innovation frameworks from the genomics age may need reevaluation when applied to proteomics-based diagnostics, since proteomics tests may need to be ordered more than once at different times or contexts by the clinicians. In this regard, evidence based criteria based on biological or clinical plausibility should drive the evolution of biotechnologies such as proteomics, rather than a sole isolated focus on the technology *per se*. Ultimately, proteomics may offer a much needed perspective to evaluate the plasticity of human physiology in health and disease, i.e., time or context dependent changes in protein expression and attendant impacts on the function of the cell and whole organisms and ecosystems.

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ABBREVIATIONS

2DE = Two-dimensional electrophoresis
GC-HPP = Gene-Centric Human Proteome Project
HUPO = Human Proteome Organization
HLPP = Human Liver Proteome Project
IASP = Integrated analytical system for proteome variation
MRM = Multiple reaction monitoring
MS = Mass Spectrometry
PSI = HUPO Proteomics Standards Initiative
PTM = Post-translational modifications
SRM = Single reaction monitoring

DUALITY/CONFLICT OF INTERESTS

None declared/applicable

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